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On the Cusp

Current Challenges and Promises in Psychiatry

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Abstract

Modern psychiatry seeks to treat disorders of the brain, the most complex and least understood organ in the human body. This complexity poses a set of challenges that make progress in psychiatric research particularly difficult, despite the development of several promising novel avenues of research. New tools that explore the neural basis of behavior have accelerated the discovery in neuroscience, yet discovery into better psychiatric treatments has not kept pace. This chapter focuses on this disconnect between the challenges and promises of psychiatric neuroscience. It highlights the need for diagnostic nosology, biomarkers, and better treatments in psychiatry, and discusses three promising conceptual advances in psychiatric neuroscience. It holds that rigorous theory is needed to address the challenges faced by psychiatrists.

Introduction

Psychiatry attempts to treat mental disorders. Modern psychiatry recognizes that since all mental phenomena are products of the brain, it follows that psychiatry attempts to treat disorders of the brain, the most complex and least understood organ in the human body. In their everyday practice, psychiatrists face a set of challenges that are fundamental to how they care for patients. Nearly every element of the clinical endeavor—from diagnosis, to treatment selection, to monitoring efficacy, to maximizing stability—is fraught with uncertainty. Diagnoses rarely represent specific entities; treatment selection is more like educated guesswork than evidence-based decision making; treatments are at best partially effective; and there are neither objective measures of treatment response nor clear paths to a cure. Although many patients benefit tremendously from the various treatments psychiatrists have at their disposal,

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many others are left with intractable symptoms that cause considerable morbidity and mortality.

These challenges, while not unique to psychiatric disorders, are driven by the complexity of the brain. This complexity is manifest at multiple levels. At the genetic level, the incredible diversity of cell types, gene expression profiles, and developmental progressions prevents simplistic genotype-phenotype correlations. At the physiological level, linking specific brain processes or physiological states to specific symptoms has been confounded by multiple factors, including a lack of understanding of how circuits perform or how these circuits are wired together. At the level of symptoms, the complexity of human mental phenomena and a relatively poorly developed tool set leaves us without clear ideas of how to characterize and study patients' experiences. Finally, there is the added complexity of how these various levels are bridged—there are multiple potential routes from genes to circuits, and from circuits to behavior.

Despite these challenges, there has been recent cause for optimism. New tools for exploring the neural basis of behavior have revolutionized neuroscience. Novel functional and structural neuroimaging technologies allow us to peer into the brains of patients even as they experience symptoms. Large-scale genetic studies identify literally hundreds of susceptibility genes that correlate with risk for psychiatric disease. Increasingly powerful tools permit the observation and manipulation of neurons and neural circuits in model organisms with exquisite specificity. These tools have facilitated an accelerating pace of discovery in neuroscience over the past two decades.

Yet the pace of discovery in psychiatric treatments has not accelerated. Rather, it has stagnated. Virtually no mechanistically novel treatments have emerged from this explosion in neuroscience. Many drug companies have completely abandoned their psychiatric drug development pipelines, while others have so radically restructured their endeavors that they appear to be starting from scratch.

In this introductory chapter, we focus on the disconnect between the challenges and promises of psychiatric neuroscience. We explore three specific challenges that psychiatry faces. First, psychiatry needs a more accurate, more neurobiologically based, *diagnostic nosology*: before one can treat a disorder, one must know what the disorder is. Second, an informed clinical practice requires *biomarkers*, measurable indicators that are associated with disorders and/or track treatment response. Third, psychiatry needs *better treatments* with enhanced efficacy and reduced side effects. Addressing these challenges would dramatically improve the practice of psychiatry.

After considering these challenges, we discuss three promising conceptual advances in psychiatric neuroscience. First is the notion of *genetics as destiny*. The veritable explosion in genetic information, facilitated by large collaborations and even larger data sets, is clarifying the role of genetic risk in the etiology of many psychiatric disorders. Second, modern neuroscience techniques

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have led to the clear demonstration that *circuits drive behavior*, inspiring efforts to characterize circuit-level disturbances in patients and in animal models of psychiatric disease. Finally, we will consider *personalized medicine*, which presupposes that quantifiable factors can guide treatment selection and predict treatment response on an individual basis. These three areas are currently the focus of intense effort; the extent to which these efforts can impact on the three challenges above may determine whether psychiatry can overcome the complexity of the brain.

This discussion leads directly into the second chapter (Redish and Gordon, this volume), which will open up discussion on how computational neuroscience might contribute to psychiatry. The premise behind these introductory chapters is that rigorous theory can help fulfill the promises of modern psychiatry in addressing the challenges psychiatrists face. The remainder of the book offers a more detailed, and hopefully compelling, consideration of this premise.

Challenges

Challenge 1: Diagnostic Nosology

A proper diagnosis serves as a crucial starting point in the patient–physician relationship. It determines how the physician approaches the patient, predicts the course and outcome of the illness, and guides treatment planning. Ideally, diagnoses are defined as part of a disease-categorizing system—a nosology—that defines an illness in a manner that is true to its biology. Individuals assigned a given diagnosis should share some common biological feature, or set of features. A diagnosis might imply a specific etiology (e.g., a gene, infectious agent, or dietary deficiency) or a specific pathophysiology (e.g., loss of insulin-secreting cells, elevated blood pressure, or uncontrolled cellular replication). The biological feature serves as a point of attack that allows the physician to understand something about the illness; a biological cornerstone around which the physician can construct a patient-specific care plan. In addition and particularly important for our discussion, the biological feature can serve as an important starting point for research aimed at improving patient care.

Psychiatric nosology lacks these cornerstones. It is not built around biology; rather, it is built upon symptoms. The classification system psychiatrists use today, codified in the fifth edition of the Diagnostic and Statistical Manual (APA 2013), relies on symptom lists. If you have two or more psychotic symptoms (delusions, hallucinations, thought disorder, catatonia, amotivation/flat affect) for at least one month, you have "schizophrenia." If you have five or more depressive symptoms (depressed mood, decreased enjoyment, weight change, sleep change, low energy, feelings of worthlessness, decreased concentration, thoughts of death) for at least two weeks, you have "major depressive

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disorder." On the face of it, establishing a diagnosis involves checking off symptom lists; for research especially, structured clinical interviews built around these symptom lists are the basis for categorizing individual patient presentations into disorders.

In many ways, this system works well. First and foremost, it provides a framework for classifying patients upon which psychiatrists can agree. It has a high degree of inter-rater reliability, at least as high as many "medical" diagnoses (Pies 2007; Freedman et al. 2013). Second it helps guide treatment and research into new treatments. Diagnostic categories suggest classes of treatments (antipsychotics for schizophrenia; antidepressants for depression), and those treatments can be reasonably effective: antipsychotics reduce psychotic symptoms in 30–70% of patients with schizophrenia (Miyamoto et al. 2002; Lieberman et al. 2005); antidepressants induce remission in 35–40% of patients with major depressive disorder and significant improvement in 50–60% (Rush et al. 2006a). Furthermore, since there is a good inter-rater reliability, research done on a particular diagnostic category can be compared across research groups in a straightforward manner. The results of such studies can often be applied to patients who meet criteria for that category with reasonable expectation of success. Finally, diagnoses are often extremely helpful for patients, allowing them to see that they are not alone in their suffering, and giving them a label to hold on to. The importance of this last point should not be underestimated, especially for psychiatric patients. Naming what they have provides immense comfort to many patients, who otherwise blame themselves for problems and symptoms they often see as integral with their personalities and sense of selves.

In other ways, the current diagnostic nosology does not work nearly so well. Categories have multiple, overlapping symptoms. For example, sleep disturbances are an official diagnostic criterion for major depressive disorder, bipolar disorder, posttraumatic stress disorder, and primary sleep-wake disorders, yet sleep disturbances are also found in other disorders, even if they are not part of the official criteria. The practical impact of this symptom overlap is high rates of comorbidity; some studies estimate that as many as 75% of patients with major depressive disorder are also diagnosed with an anxiety disorder at some point in their lifetime (Lamers et al. 2011). Moreover, some fraction of patients seeking help do not clearly meet criteria for any given disorder, resulting in "catch-all" categories such as "anxiety disorder NOS" (i.e., not otherwise specified). These and other issues decrease the ability of the physician to make reliable predictions as to the course of an illness and the response to treatment, since many patients do not match the "pure" forms of diagnoses typically studied in research protocols.

Perhaps the most troubling aspect of the current diagnostic nosology for psychiatric disorders is the lack of biological relevance. Over and over, attempts to characterize biological correlates of diagnostic categories have by and large failed. Biomarkers based in biology were among the first to be

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studied; they fail, however, to adhere reliably to disorder boundaries (see below). Modern imaging studies are little different: multiple anxiety, mood, and substance use disorders show enhanced activity in the amygdala (Gilpin et al. 2014); posttraumatic stress disorder, schizophrenia, and depression are all associated with decreased size of the hippocampus (Videbech and Ravnkilde 2004; Smith 2005; Adriano et al. 2012). Similarly, early family studies that demonstrated heritability of psychiatric disease risk showed that genetic risk factors typically predisposed to multiple disorders (Kendler 2006). This is true even for large pedigrees with defined genetic lesions of relatively large effect, such as the Scottish DISC1 translocation pedigree (Brandon and Sawa 2011). Modern molecular genetics confirms what was already known from the family studies at the single gene level: many specific genetic lesions raise risk for multiple diagnoses (Intl. Schizophrenia Consortium 2009; Williams et al. 2011). For example, a calcium channel gene, *CACNA1C*, increases risk for both bipolar disorder and schizophrenia (Green et al. 2010; Curtis et al. 2011); a microdeletion on chromosome 22 raises risk for both autism and schizophrenia, among other psychiatric diagnoses (Schneider et al. 2014). The bulk of the biological evidence makes it very clear that our current diagnostic categories are missing the mark in terms of carving out psychiatric disease at its neurobiological joints.

Challenge 2: Biomarkers

Biomarkers of disease can be the key to accurate diagnosis and optimal treatment. Think of hemoglobin A1c levels in diabetes.[1] This marker, elevated in patients with chronic uncontrolled diabetes, gives an indication of how dysregulated blood glucose levels have been over the recent past. It is key to the diagnosis of diabetes, particularly type II diabetes, the kind with (usually) adult onset and an association with obesity. Like psychiatric disorders, type II diabetes is of complex etiology, with multiple small effect genetic risk factors and a host of possible environmental precipitants. Yet unlike psychiatric disorders, the diagnosis is made more straightforward by testing for hemoglobin A1c levels. Should these levels rise above a threshold, the physician and patient can discuss various interventions. However, the utility of this biomarker does not end with diagnosis. Proper management of blood glucose will result in a gradual decline in hemoglobin A1c levels. By monitoring these levels regularly, the efficacy of the treatment can be tracked over time.

Considerable effort has been expended to try and develop biomarkers for psychiatric disease that might be similarly useful. Among the earliest biomarkers were neuroendocrine markers, such as dysregulation of the glucocorticoid system for major depressive disorder (Plotsky et al. 1998). The dexamethasone

[1] http://www.webmd.com/diabetes/guide/glycated-hemoglobin-test-hba1c (accessed May 5, 2016).

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suppression test was one of the first tests to be proposed for any psychiatric disease (Kalin et al. 1981; Hayes and Ettigi 1983). It takes advantage of the negative feedback system instantiated in the hypothalamic-pituitary-adrenal axis; exogenous glucocorticoids (dexamethasone) induce a downregulation of endogenous cortisone. Patients with depression have a relative failure to downregulate cortisone in response to exogenous dexamethasone. However, the dexamethasone suppression test has relatively poor sensitivity (as low as 40–60%) and specificity (as low as 70%) and has not proven useful in clinical prediction (APA Task Force on Laboratory Tests in Psychiatry 1987).

Similar issues have befallen other attempts to develop biomarkers using various modalities. Neurophysiological biomarkers examining, for example, electroencephalographic activity at baseline or in response to various stimulation paradigms have been proposed for schizophrenia (Rosen et al. 2015). Similarly, neurobehavioral tests, such as smooth pursuit eye movements, have been touted as likely possibilities (Calkins and Iacono 2000). Neither has led to usable biomarkers, either due to a failure to reliably distinguish controls and patients when tested broadly, or because of a lack of specificity for schizophrenia. Moreover, several such tests demonstrate schizophrenia-related phenotypes in unaffected relatives. This can be advantageous in that it suggests that these biomarkers reflect the underlying traits that correlate with schizophrenia susceptibility. However, the presence of a biomarker in unaffected relatives suggests limited utility for differentiating individuals with schizophrenia from those with other diagnoses, and for the state of the patient during treatment.

The advent of neuroimaging has led to increasingly sophisticated attempts to utilize patterns of brain structure or activity as biomarkers for psychiatric illness. Here some studies have demonstrated effects of treatment. For example, successful treatment of intractable depression results in the reversal of abnormal patterns of activity in the medial prefrontal cortex, regardless of the type of treatment that was used (Mayberg et al. 1999). Similarly, both psychotherapy and medication treatment of obsessive-compulsive disorder reverses abnormal patterns of activity in the striatum (Baxter et al. 1992). Nonetheless, the general applicability of these findings to clinical situations is unclear. Moreover, as noted above, numerous imaging findings have proven to be nonspecific, with considerable overlap even between seemingly disparate psychiatric disorders.

One possibility for improving upon traditional biomarker studies would be to combine multiple biomarkers and compare across diagnoses. While attempts to do so have not met with success in the past, increasing the power of biomarker studies by using larger data sets, as has been done for genetic studies, may yet meet success (Schwarz and Bahn 2008). Currently, however, it is unclear whether such approaches will yield the kind of useful biomarkers that would aid clinicians in their attempts to diagnose and treat patients.

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Challenge 3: Treatments

For psychiatry, treatments are a relative success story. Dopamine 2 receptor-blocking antipsychotics, lithium and other stabilizers, monaminergic boosters, and benzodiazepines have been relatively successful in treating schizophrenia, bipolar disorder, depression, and anxiety, respectively. In addition, there are now many well-studied, tailored psychotherapies for a variety of psychiatric conditions. The best can be at least as efficacious as medication, and for some conditions (e.g., obsessive-compulsive disorder) they can be even better (Foa et al. 2005). Finally, electroconvulsive therapy (ECT) has established itself as a bona fide treatment for mood disorders with proven efficacy (McDonald et al. 2002). Other somatic therapies, from magnetic stimulation to deep brain stimulation, may not be far behind.

Yet for all this success, treatment remains inadequate for many patients, particularly in real-world situations. Most academic studies report treatment response rates of 50–90%. Responses represent significant improvement, which itself is typically defined as some threshold decrease in symptoms, scored on a standardized scale to reduce subjectivity. Remission rates are considerably lower. Remission requires the symptom scores to be lower than would be required to make the diagnosis in the first place. Most clinicians would consider remission to be the goal with their patients, where possible. In most academic studies, remission is achieved only 30–60%, though of course these rates vary by disease and the population studied. Clinical studies that attempt to mimic real-world clinical situations (by allowing for complicating factors such as comorbid conditions) have even lower rates. For example, in two large U.S. trials, one for depression and one for schizophrenia, remission rates were 30% and 15%, respectively (Sinyor et al. 2010; Levine et al. 2011b). Although some individual treatments for specific disorders can achieve higher rates (response rates to ECT for depression can be as high as 90%; Petrides et al. 2001), on the whole, available therapies leave many psychiatric patients inadequately treated.

Of course, even once remitted, psychiatric disorders can relapse. Relapse rates for most major psychiatric disorders are quite high: 10-year relapse rates for patients successfully treated with antidepressants are as high as 90% if patients stop their medication (Boland and Keller 2002). Even continuing medication is no guarantee of remaining well. Relapse rates on (previously effective) mood stabilizers, for example, can be as high as 50% (Keck and Manji 2002).

Even when current treatments work, tolerability becomes a significant issue. Side effects of psychiatric medications can be considerable. For antipsychotic medications, weight gain, hyperglycemia, and motor symptoms can be significant. For antidepressants, weight gain and sexual dysfunction are often given as reasons why medications are dropped. Anxiolytic medications can be addictive. In addition, tolerability is not just an issue for medication. Many patients have considerable memory loss with ECT, and compliance with

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psychotherapies can be difficult. The costs in time and money of psychotherapy are also of concern to some patients. Finally, few psychiatric medications work quickly; many take weeks or even a few months to exert their effects, leaving patients suffering considerably even after treatment has been started.

Given the considerable weaknesses of currently available treatments for psychiatric disorders, one would expect considerable activity aimed at improving upon them. Unfortunately, there has been little truly novel treatment development for some time. Most current medications were either discovered to be efficacious by happenstance—like the first antipsychotics, mood stabilizers and antidepressants, which were all under study for other purposes before accidentally being found to be helpful in their respective areas—or are "me-too" drugs designed to tweak the molecular structure of existing drugs but relying on the same underlying mechanism. Even research in somatic and psychological treatments suffers from the me-too problem, with the successful treatment-du-jour being tried repeatedly for a number of different disorders, on the premise that if it works for one thing, it just might work for them all. Meanwhile, as noted above, pharmaceutical companies have little in the development pipeline after multiple, high-cost failures (Insel 2011). Part of the issue is the difficulty of translating findings from animal models into the human; the history of innovation in psychiatric pharmacotherapy is littered with examples of therapeutics that worked wonderfully in rodent models but failed in clinical trials (Hyman 2014).

Promises

Promise 1: Genetics as Destiny

Psychiatric disorders are overwhelmingly familial, with inheritance rates estimated at 30–70%, depending on the diagnosis (Kendler 2006). Understanding this inherited risk has been incredibly difficult. For a long time it was not at all clear where the destiny of psychiatric genetics led: to the holy grail of a thorough understanding of the neurobiological basis for psychiatric disease, or the trash heap of promising but eventually discarded technological advances. Early attempts at identifying psychiatric risk genes failed, with a few notable exceptions, such as Huntington disease and some Mendelian forms of autism. Several factors contributed to these failures, including incorrect assumptions about the form of genetic risk (simple vs. complex genetics), as well as the fact that genetics crosses diagnostic boundaries, as noted above. More recently, some success has been made in identifying the genes that contribute to disease risk, but this has not yet had an impact on psychiatric practice.

Gene identification has benefited from several developments. First, the genomic era has dramatically reduced the price of genotyping while increasing its speed and accuracy. Second, geneticists have realized that progress requires

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enormous sample sizes, which are facilitated by these technical advances. Third, these same geneticists have formed large international collaborations to generate samples of sufficient size to carry out such studies. One recent genome-wide study of schizophrenia used samples of nearly 40,000 cases and over 100,000 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

With this increase in scale comes a greater understanding of the landscape of genetic risk, at least for schizophrenia and autism. Risk genes fall into two categories: common alleles of small effect size and rare alleles of large effect size. The common alleles are frequently present in the general population; any one risk allele raises the risk of disease only slightly (on the order of a few percentage points increased risk). The 108 loci identified in the above study are of this sort, each conferring a very small amount of risk; estimates based on modeling suggest that there may be as many as 2000 risk loci of the common allele, small effect size variety for schizophrenia.

The rare alleles occur very infrequently in the general population, often arising *de novo* in the patient and not inherited from either parent. The presence of one of these rare alleles signifies a considerable increase in risk—as much as 30-fold (3000%!) (Karayiorgou et al. 1995). Many of these rare alleles are copy number variants (large deletions or duplications of many genes). Others are sequence variants identified only with whole exome (all expressed genetic material) sequencing. It is unclear how many of these rare variants exist; for autism, hundreds have already been identified (Sebat et al. 2007; Levy et al. 2011; Iossifov et al. 2014).

Of course, feeding into this complexity is the fact that these genetic studies are being conducted on samples derived from current diagnostic criteria, which as noted above are crude. At least part of the complexity might be reduced by an improved diagnostic system. Indeed, it may be that genetic information could be used to improve diagnostic nosology, given that it is inherently biological. The complexity of the genetic landscape may be already apparent in the numbers of identified genes, which provide an embarrassment of riches to those wishing to use the clues to unravel the neurobiology of psychiatric illness noted above. Yet the sheer number of genes represents only the tip of the iceberg in terms of complexity. The relationship between genotype and phenotype is likely to be complex. A given gene can result in different psychiatric phenotypes in different patients, and nearly identical phenotypes can be caused by remarkably different genotypes. Gene–environment interactions and epigenetic modifiers complicate matters even further.

Methods are needed to address this complexity. The first attempts have been aimed at organizing these large numbers of genes into pathways and networks, so that their effects on biology can be understood. But these attempts are far removed from the behavioral endpoints of psychiatric disease. In the end, translation from genetics to behavior occurs through neural structures, which are fundamentally about the computations that support behavior. Understanding

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this translation will be fundamental to demonstrating how genetics influence risk for psychiatric disease.

Promise 2: Circuits Drive Behavior

Increasingly, the focus of neuroscientists trying to understand how the brain produces behavior has been drawn to the level of the neural circuit. Neural circuits may be localized within a given brain region or distributed across several areas. Their building blocks are neurons of various, specific types, as well as the neural processes and synapses that connect them. Circuits have the potential to carry out neural computations; that is, to take in information, transform that information into commands, and output those commands appropriately, driving behavior. The ascendency of circuit-based analyses in neuroscience has led to the corresponding circuit hypothesis of psychiatric disease, in which abnormal function of neural circuits leads to psychiatric symptomatology (Ressler and Mayberg 2007; Akil et al. 2010). Methods to change circuit function thus become more than just research tools, but potential therapies.

This focus on circuits has been driven by technological advances in animal models. Anatomical techniques, starting with Golgi and Ramon y Cajal and progressing to engineered viruses and specialized tissue processing and microscopy techniques, enable a description of the fine details of neurons and the connections which make up circuits. Physiology, beginning with electrophysiology but now including fluorescent activity indicators, permits the monitoring of these circuits with exquisite specificity. Genetic manipulation and molecular biology facilitate increasing knowledge regarding the cellular machinery underlying the formation and maintenance of circuitry. More recently, optogenetic and pharmacogenetic technology permits the manipulation of circuit function with cellular, anatomical, and temporal specificity. Using these tools, the precise wiring diagram for a given circuit can be mapped, the activity patterns of each of the elements in the circuit can be monitored during behavior, and these patterns can be mimicked or interrupted to test whether they are necessary and/or sufficient for the behavior.

A considerable amount of these efforts are directed at circuits and behaviors with relevance to psychiatry, albeit in animal models. Studies of depression- and anxiety-like behaviors have implicated amygdala and prefrontal circuits as well as neuromodulatory centers (Tye et al. 2011, 2013). The circuits underlying social behavior have been explored, with attention paid to some of these same brain regions (Yizhar 2012). Cognitive behaviors disrupted in schizophrenia, particularly working memory and executive function, have also been examined (Cho et al. 2015; Spellman and Gordon 2015). The rapidly expanding tool set of the circuit neuroscientist has given traction to efforts to understand the complex neurobiology underlying these phenomena. Importantly, these findings demonstrate that the key building block of behavior is the neural circuit. Perhaps more importantly for psychiatrists, they also show that one can

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have tremendous impacts on behavioral output with relatively specific manipulations at the circuit level.

Meanwhile, cutting-edge clinical work would suggest that the focus on circuits might translate to patients and be useful to clinicians. Neuroimaging studies clearly point out that these same brain regions, important for specific behaviors in the rodent, are engaged in humans in similar tasks, and often are dysregulated in patients. Moreover, imaging and other experiments in humans can help make the connection between circuit function and subjective experiences that play such an important role in psychiatric disorders and yet can be challenging to study in animal models. Finally, studies of the effects of various therapies—whether pharmacological, psychotherapeutic, or brain stimulation—demonstrate that it is possible to modulate activity at the level of the (macro) circuit in humans (Baxter et al. 1992; Mayberg et al. 1999).

Promise 3: Personalized Medicine

Personalized medicine is a movement throughout the entire field of medicine to tailor therapy to the individual patient. In some ways this is an old idea, expressed in a new way. A physician has many options to offer to treat the hypertensive patient. One guide can be simply taking the patient's pulse. Patients with hypertension and low resting heart rate tend not to respond well to beta blockers, drugs that block the beta-adrenergic receptor. For such a patient, choosing an alternative medicine represents a form of personalized medicine.

The modern advance is to consider not just the specifics of the illness but the specifics of the patient as well. For example, certain patients metabolize certain medications faster, or slower, meaning that doses should be adjusted or medications avoided. Metabolizer types could be identified from the genome or tested biochemically. Beyond metabolism, biomarkers could help stratify patients into those more likely to contract a specific subtype of an illness, and/or respond to a particular treatment.

Currently in psychiatry, treatment selection is not guided by such information. Patients are evaluated and diagnosed, and treatments are applied to symptoms. But the selection of a given treatment has more to do with the avoidance of side effects (e.g., a patient's preference weight gain or insomnia) than with the efficacy of the medication for any particular kind of patient. Better diagnostics would help, if improved diagnostics would lead to improved predictions about treatment responses. But even in the absence of improved diagnostics, it may be that certain biomarkers—genetic or otherwise—would help guide treatment selection in a meaningful way.

There are some examples of this kind of research in psychiatry. For example, early behavioral subtyping of depression led to the demonstration that patients with atypical depression, which is characterized by mood reactivity, will respond better to monoamine oxidase inhibitors than to tricyclic antidepressants (Liebowitz et al. 1988). The true promise of personalized medicine is

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that buried somewhere in the immense data sets being collected lies the secret to determining which treatment will result in the best response for a particular, individual patient.

Waiting for Godot

The disconnect between the promises and challenges of psychiatric neuroscience begs for a solution, for a savior—some breakthrough that will solve all the problems of psychiatry in one fell swoop. Indeed, the history of psychiatric research is riddled with failed saviors, from psychoanalysis to behaviorism, to pharmacology, to neuroimaging, to molecular genetics, each hailed by its own generation as the miracle that will help us define and understand mental illness.

The truth is that there are no saviors. No all-encompassing breakthrough will lead us down the garden path toward improved understanding and better treatments. The complexity of the brain stands in our way. Psychiatric disorders are the products of hundreds of genes and thousands of cell types and millions of connections. Answers will surely not come from one sole technological advance, and they will most assuredly be as complex as the questions.

Nonetheless, computational neuroscience may be poised to influence the field, to help the promises of psychiatry overcome the challenges. Genetics has generated lists of hundreds of genes that raise risk for schizophrenia, autism, and other psychiatric disorders. How can we organize and understand these genes? Circuits are the fundamental building blocks of behavior. How can we understand which circuits are broken in mental illness? How can we learn enough about these circuits to repair them? Finally, patients may respond better if therapies are tailored to their unique biology. How do we learn enough about any individual patient to guide treatment appropriately?

In this volume, we explore the potential role that computational approaches can play in addressing these questions. We will wonder openly whether and how understanding the biological system of the brain through a set of rigorously constructed and quantitatively tested theoretical constructs will help clarify diagnostic issues by identifying where these biological systems can break down. We will contemplate how such an approach could lead to biologically and pathophysiologically relevant biomarkers. We will attempt to generate ideas about how psychiatry can help models become more focused on issues of importance to patients and physicians. And we will speculate on what a success might look like, what form the first "killer app" of computational psychiatry neuroscience might take. We know that computational psychiatry will not be the next savior, but we hope, at least, that failure might be averted through a careful consideration of how to use computational approaches to address the challenges psychiatry faces.

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